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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/602,800	06/23/2000	David B. Agus	P1760R1	1759

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/602,800	Applicant(s) AGUS ET AL.	
	Examiner Anne Holleran	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 22-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 22-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed April 1, 2003 is acknowledged. Claim 31 was added. Claim 10 was canceled.

2. Claims 1-9 and 22-31 are pending and examined on the merits.

3. In view of the papers filed April 1 (Petition to Correct Inventorship under 1.48(b) and June 23, 2000 (authorization to charge fees under 37 CFR 1.17), the inventorship in this nonprovisional application has been changed by the deletion of inventors David B. Agus and Howard I. Sher.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Claim Rejections Withdrawn:

4. The rejection of claims 4, 5 and 22-30 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

5. The rejection of claims 1-9 under 35 U.S.C. 112, first paragraph, is withdrawn upon further consideration.

6. The rejection of claims 1, 6, and 8-9 under 35 U.S.C. 102(b) as being anticipated by Curnow, Cancer Immunology Immunotherapy, Vol. 45, pages 210-215, 1997 is withdrawn upon further consideration.

Claim Rejections Maintained and New Grounds of Rejection:

7. Claims 1-9 and 22-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the amendment to claim 1 and 31 introduces new matter into the specification. Furthermore, the specification fails to provide written description of antibodies which block ligand activation of an ErbB receptor more effectively than monoclonal antibody 4D5, in view of the specification's definition of "monoclonal antibody 4D5".

The amendment introduces new matter into the specification, because the specification only provides support for contemplation of methods where the antibody to be used in the claimed methods blocks ligand activationof an ErbB receptor *substantially* more effectively than monoclonal antibody 4D5. Thus, the specification describes methods where there is substantial difference between the activity of the antibody to be used in the claimed methods compared to the activity of monoclonal activity 4D5, whereas the claimed methods are drawn to methods where the antibody to be used in the claimed methods may exhibit even a very slight difference in activity when compared to monoclonal antibody 4D5.

Secondly, the claimed inventions lack written description because the specification describes the term "monoclonal antibody 4D5" as an antibody that has antigen binding residues of, or derived from, the murine 4D5 antibody (ATCC CRL 10463). Therefore, the monoclonal antibody 4D5, as currently recited in the claims, may be one that has very little in common structurally with the murine antibody 4D5 (ATCC CRL 10463), and may have very low binding affinity for Her-2 and may not have any effect on cell proliferation. For example, the specification also cites U.S. Patent 5,821,337, which describes humanized versions of the murine antibody 4D5 (ATCC CRL 10463), where some of the humanized versions do not have any effect or very little effect on cell proliferation. In view of the definition of the 4D5 antibody, it appears that the claimed methods comprise the use of an antibody that may be functionally compared to an antibody that has very little in common with the one antibody that was used in working examples (trastuzumab, huMab 4D5-8). Therefore, the examples in the specification are not representative of the full scope of the claims.

Claims that recite monoclonal antibody 2C4 are also not described because the definition of this antibody is also very broad and includes variants of monoclonal antibody 2C4 (ATCC HB12697), such as antibodies that have antigen binding residues of, or derived from the murine monoclonal antibody 2C4 (ATCC HB12697). In view of the broad definition, which includes antibodies with antigen binding residues that are "derived from" murine monoclonal antibody 2C4 (ATCC HB12697) without saying how many, or which, or in which arrangement, these residues are "derived from" murine monoclonal antibody 2C4 (ATCC HB12697), the term monoclonal antibody 2C4 without the reference ATCC number appears to refer to almost any antibody that might bind to Her-2.

Therefore, the claims are not supported by the specification as originally filed because the amendment introduces new matter, and because the full scope of the claimed methods comprising the administration of inadequately described antibodies, is not described. Therefore, it does not appear that applicant was in possession of the invention as claimed at the time the application was filed.

8. Claims 1-9 and 22-28, 30 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Ross I (U.S Pre-Grant Publication 2002/0076695; published June 20, 2002; effective filing Sep. 14, 1998) as evidenced by Reese (Reese, D. et al. Proceedings of the American Association for Cancer Research, 37: page 51, March 1996; Abstract #353).

As discussed above, the claimed inventions are drawn to methods for the treatment of cancer, comprising the administration of an antibody that binds to Her-2. The references in the claims to comparison with monoclonal antibody 4D5, or the reference to monoclonal antibody 2C4, do not limit the claimed inventions, in view of the definition provided in the specification for the scope of these terms, such that these terms include antibodies comprising derivatives of the referenced antibody.

Ross I teaches methods for the treatment of prostate cancer, and contemplates treating both androgen-dependent and androgen independent prostate cancers (see page 4-5, paragraphs 38 – 40). Ross I teaches methods of treatment comprising the administration of anti-Her2 antibodies, and also specifically the administration of Herceptin® (rhumab4D5-8) (see page 2, paragraph 19), which is an antibody that blocks ligand activation of an ErbB receptor, and therefore, would be an antibody that blocks TGF-α activation of MAPK and would be an

antibody that blocks the formation of an ErbB hetero-oligomer (as evidenced by Reese). Ross teaches the use of antibody fragments and humanized antibodies (see claims 2 and 3, page 6).

9. Claims 1-9 and 22-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak (U.S. Patent 5,725,856; issued 03/1998; effective filing date 01/1988) and Ross II (U.S. Patent 5,994,071; issued 11/1999; filing 04/1997); in view of Sliwkowsky (Sliwkowsky, M.X. et al, J. Biol. Chem. 269: 14661-14665, 1994) or Klapper (Klapper, L.N. et al. Oncogene, 14: 2099-2109, 1997); and further in view of Plowman (U.S. Patent 5,804,396; issued 09/1998; effective filing 10/1994) or Akita (U.S. Patent 5,968,511; issued 10/1999; effective filing 03/1996) or Greene (U.S. Patent 6,417,168; issued 07/2002; effective filing 03/1998).

The claimed inventions are drawn to methods for the treatment of prostate cancer comprising the administration of antibodies that inhibit ligand activation of an ErbB receptor. Hudziak teaches methods of inibiting the growth of tumor cells by administering to a patient antibodies capable of inhibiting Her2 (ErbB2) function, and teaches methods of inhibiting the growth of tumor cells that overexpress a growth factor receptor (see col. 4, lines3-31). Hudziak fails to appreciate that prostate cancer cells would be a target. Ross II teaches prostate cancer cells over express ErbB2 (see col. 6, lines 25 – 51), and that expression of ErbB2 is associated with poor prognosis in prostate cancer. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used anti ErbB2 antibodies that inhibited the function of ErbB2 for the treatment of prostate cancer.

While the combination of Huziak and Ross II teaches generally methods for the treatment of prostate cancer comprising the use of antibodies that bind to ErbB2, and Hudziak

contemplates antibodies that bind to ErbB2 and inhibit ligand binding to an ErbB growth factor receptor, or the down regulation of the growth factor (see col.5, lines 38-64), the combination of Hudziak and Ross fail to specifically teach methods comprising the use of antibodies that inhibit the formation of an ErbB hetero-oligomer. However, such antibodies are known in the art, as evidenced by the teachings of Sliwkowsky that monoclonal antibody 2C4 inhibits the activation of ErbB2 by heregulin (see page 14663, 1st col.). Also, Klapper teaches antibodies that bind to ErbB2 and inhibit interaction of ErbB2 with other ErbB receptors (see pages 2102 –2105). Additionally, the prior art, as evidenced by Plowman, Akita and Greene, recognizes that the inhibition of ErbB2 oligomerization with other ErbB receptors is a therapeutic target for the treatment of cancer. Plowman teaches thereapeutic agents that inhibit signal transduction by Her-2 heterodimers (see abstract and col. 4, lines 31-49). Akita teaches antibodies that bind to ErbB3 that inhibit the binding of heregulin-induced formation of an ErbB2-ErbB3 heteroligomer, and teaches the use of such antibodies in the treatment of cancer (prostate cancer is contemplated), in which excessive activation of the ErbB2-ErbB3 complex is occurring (see abstract, and col. 29, lines 9 – 23). Greene teaches methods for treatment of cancer comprising administering a peptide that inhibits the formation of ErbB protein dimers, where the dimers may be heterodimers (see claims 1 and 14; and col. 9, lines 15-21).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the antibodies of either Sliwkowsky or Klapper in the method of Hudziak for the treatment of prostate cancer. One would have been motivated to use antibodies that inhibited ligand activation of an ErbB receptor in view of the fact that the art

recognized that ErbB2 was activated by the formation of heterodimers and that ErbB2 activation plays a role in the growth of prostate cancer cells.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-9 and 22-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-40, and 42-62 of copending Application No. 08/948,149. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of Application No. 08/948,149 are drawn to methods for inducing cell death comprising exposing a cell which overexpresses ErbB2 to an effective amount of an isolated antibody that binds to an epitope on ErbB2 to which 7F3 binds. The cell may be in a mammal and mammal may be in a human. The application specifically teaches that prostate cancer is a target of the claimed methods. The monoclonal

antibody 7F3 is an antibody that inhibits heterodimerization between ErbB2 and another ErbB receptor.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 1-9 and 22-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 42, 45, 55 and 66 of copending Application No. 09/705,579. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of Application No. 09/705,579 are drawn to methods for treatment of cancer or prostate cancer comprising administering an antibody such as monoclonal antibody 7F3. The application and the claims specifically teach that prostate cancer is a target of the claimed methods. The monoclonal antibody 7F3 is an antibody that inhibits heterodimerization between ErbB2 and another ErbB receptor.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 1-9 and 22-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4-9, 16-22, 24-27, and 60-63 of copending Application No. 09/600, 812. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of Application No. 09/600,812 are drawn to methods for treating cancer with an antibody that inhibits ligand

activation of an ErbB receptor. A preferred embodiment described in the specification is prostate cancer.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
November 18, 2003